An Efficient Synthesis of Optically Active *trans*-2-Aryl-2,3-dihydrobenzofuran-3-carboxylic Acid Esters via C-H Insertion Reaction

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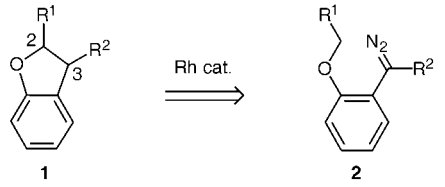
Abstract: Optically active *trans*-2-Aryl-2,3-dihydrobenzofuran-3-carboxylic acid esters were synthesized by intramolecular C-H insertion reaction. Upon treatment with a catalytic amount of Rh_2(*R*-DOSP)$_4$, aryldiazoester **8c** possessing a chiral auxiliary underwent C-H insertion reaction to give **9c** in high yield and in high selectivity (84% yield, 86% de).

Key words: dihydrobenzofuran, C-H insertion, Rh_2(*R*-DOSP)$_4$, chiral auxiliary, pyrrolidinyl lactamide

2,3-Dihydrobenzofuran (coumaran) **1** is a basic skeleton found in a number of biologically interesting compounds. Furthermore, 2-aryl-2,3-dihydrobenzofuran-3-carboxylic acid derivatives (**1**: R^1 = Ar, R^2 = CO_2R) constitute the major frameworks of such natural products as neolignans,[1] serotobenine (**3**)[2] and (–)-ephedradine A (**4**)[3] (Scheme 1, Figure 1). Because of the unique bioactivities, efficient methodology for the synthesis of dihydrobenzofuran has long been sought after. While extensive synthetic efforts have been reported to date, including the biomimetic, oxidative dimerisation of cinnamic acid derivatives,[4] only a handful of enantioselective syntheses are available.[5]



Scheme 1

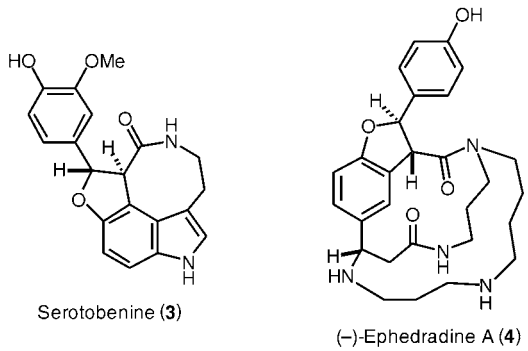
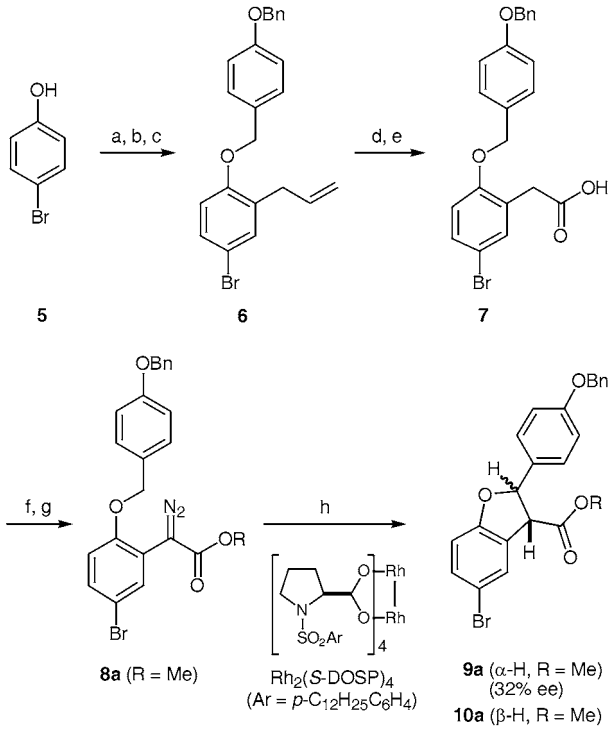


Figure 1

Asymmetric C-H insertion reaction of metal-carbenoids has been the subject of intensive investigation.[6] Davies has recently reported that a chiral rhodium-carbenoid, derived from an aryl diazoester, undergoes inter- or intramolecular asymmetric C-H insertion reaction.[7,8] We envisioned that intramolecular C-H insertion of the carbenoid generated from **2** would provide the optically active *trans*-2-aryl-2,3-dihydrobenzofuran-3-carboxylic acid esters **1** (R^1 = Ar, R^2 = CO_2R), the results of which are described herein.

As shown in Scheme 2, the diazoester **8a** was readily prepared in a seven-step sequence from 4-bromophenol (**5**). Thus, allylation of phenol **5**, Claisen rearrangement, and



Scheme 2 *Reagents and conditions*: a) Allyl bromide, K_2CO_3, DMF, 60 °C (99%); b) diethylaniline, 210 °C (88%); c) K_2CO_3, 4-(benzyloxy)benzyl chloride, DMF, 60 °C (95%); d) O_3, CH_2Cl_2/MeOH, –78 °C; Me_2S, –78 °C to r.t.; e) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4{\cdot}2H_2O$, *t*-BuOH/H_2O (77% in 2 steps); f) CH_2N_2, Et_2O (81%); g) *p*-$AcNHC_6H_4SO_2N_3$, DBU, CH_3CN (71%); h) Rh_2(*S*-DOSP)$_4$ (5 mol%), CH_2Cl_2 (72%, **9a**:**10a** = 2:3).

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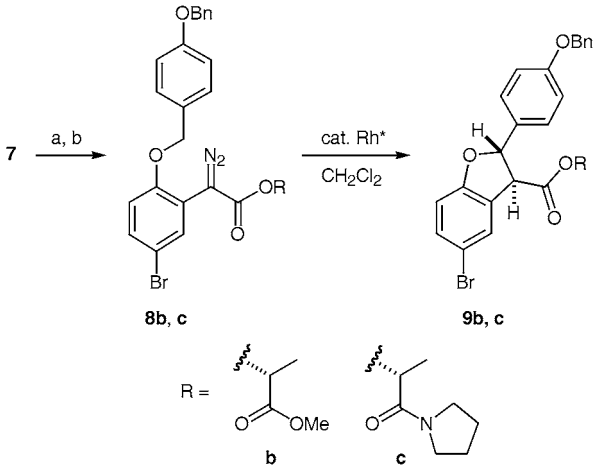
subsequent introduction of a 4-(benzyloxy)benzyl group to the resultant phenol provided **6**. Ozonolysis of the double bond in **6** followed by treatment with $NaClO_2$ furnished the carboxylic acid **7**. After esterification of **7**, diazotransfer reaction was carried out by treatment with *p*-acetamidobenzenesulfonyl azide and DBU.

With the requisite diazoester **8a** in hand, the C-H insertion reaction by chiral rhodium catalyst was next investigated. Upon treatment of **8a** with 5 mol% of Davies' catalyst, Rh_2(*S*-DOSP)$_4$, the reaction proceeded smoothly to afford the dihydrobenzofuran in 72% yield as a 2:3 mixture of **9a** and **10a**,[9] and the enantiomeric excess of the *trans*-isomer was 32%.[10] In order to improve the enantioselectivity, incorporation of a chiral auxiliary to the ester moiety of **8a** was investigated (Scheme 3).



Scheme 3 *Reagents and conditions*: a) ROH, WSCD, DMAP, CH_2Cl_2; b) *p*-$AcNHC_6H_4SO_2N_3$, DBU, CH_3CN (75% for **8b** and 73% for **8c** in 2 steps).

Table 1 Diastereoselectivity of the Rh-Carbenoid-Mediated Intramolecular C-H Insertion Reaction of **8b** and **8c**

Run	Cat. Rh[a]	**9b**[b]	**9c**[b]
1	$Rh_2(OAc)_4$	7:2	3:1
2	Rh_2(*S*-DOSP)$_4$	5:2	8:1
3	Rh_2(*R*-DOSP)$_4$	7:2	13:1

[a] All reactions were carried out in CH_2Cl_2 using 5 mol% of Rh catalyst.
[b] Diastereoselectivity was determined by ^1H NMR.

Davies reported earlier that high diastereoselectivity of intermolecular Rh-carbenoid-mediated cyclopropanation was achieved by using α-hydroxy ester derivatives as the chiral auxiliaries.[11] Similarly, we have observed high diastereoselectivity in the C-H insertion reaction when **8b** and **8c** were employed.[12] Thus, carboxylic acid **7** was coupled with methyl (*S*)-lactate and pyrrolidinyl (*S*)-lactamide[13] to give, after diazo transfer reaction, the cyclization precursors **8b** and **8c**, respectively (Scheme 2). Upon treatment with rhodium catalyst (5 mol%), the C-H insertion reactions of **8b** and **8c** proceeded smoothly to afford exclusively the *trans*-dihydrobenzofurans **9b** and **9c** (Table 1). Presumably, the increased bulk of the ester moiety is responsible for the high *trans*-selectivity. Furthermore, it is interesting to note that the C-H insertion products **9b** and **9c** possessed the same configuration (2*S*, 3*S*) regardless of the chirality of the catalyst (run 2 and 3). Thus, the asymmetric induction was solely dependent on the chiral auxiliaries and not on the catalyst.[14] The highest diastereoselectivity was attained by combination of the diazoester **8c** and Rh_2(*R*-DOSP)$_4$ to afford **9c** in 84% yield and 86% de. Basic hydrolysis of **9c** with $Ba(OH)_2$ gave the desired carboxylic acid.[15]

In conclusion, an efficient construction of optically active *trans*-2,3-dihydro-3-benzofuran derivatives was accomplished by combination of Davies' Rh catalyst and the pyrrolidinyl (*S*)-lactamide chiral auxiliary. This protocol would be amenable to large-scale preparations of the dihydrobenzofuran derivatives, because the reaction employs an inexpensive chiral auxiliary and proceeds at room temperature. In fact, during the course of synthetic study on (–)-ephedradine A (**4**), conversion of **8c** to **9c** was accomplished on a 50 g scale. Application of this methodology to the total syntheses of **3** and **4** is under investigation in our laboratories.[16]

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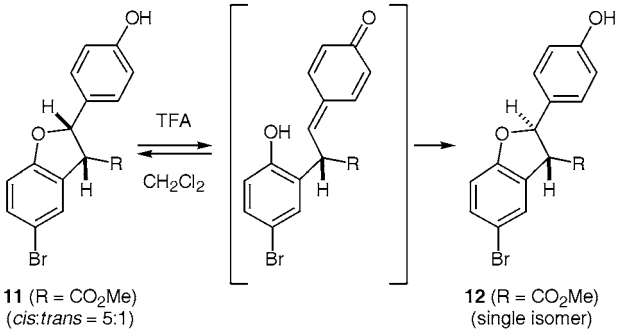
(9) The 2,3-*cis*-benzofuran was readily converted to the thermodynamically more stable *trans*-isomer as shown in Scheme 4. After removal of the benzyl group, treatment of **11** with TFA resulted in the predominant formation of the *trans* isomer **12**. The α-position of the ester **11** was unaffected during the transformation based on the fact that no deuterium incorporation was observed in **12** when **11** was treated with CF_3CO_2D in CD_2Cl_2.



Scheme 4

(10) Recently, Hashimoto reported a similar C-H insertion reaction with his Rh(II)-catalyst, which proceeded in high enantio- and diastereoselectivity: Treatment of a similar aryldiazoacetate with 1 mol% of the catalyst in toluene at –78 °C provided the *cis*-benzofuran in 94% ee, see: Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887.

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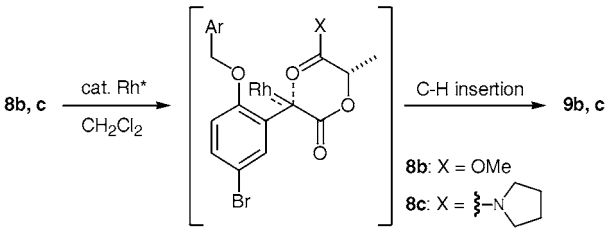
(12) The high diastereoselectivities observed with **8b** and **8c** indicate that the carbenoid intermediate might have strong interaction with the carbonyl group of the chiral auxiliary as illustrated in Scheme 5. The similar interaction was reported in ref. 10.



Scheme 5

(13) High diastereoinduction with pyrrolidinyl (*S*)-lactamide as a chiral auxiliary has been reported by Tschaen in the S_N2 reaction of α-haloester derivatives, see: Devine, P. N.; Dolling, U.-H.; Heid, R. M. Jr.; Tschaen, D. M. *Tetrahedron Lett.* **1996**, *37*, 2683.

(14) For double asymmetric induction in intramolecular C-H insertion reactions, see: Hashimoto, S.; Watanabe, N.; Kawano, K.; Ikegami, S. *Synth. Commun.* **1994**, *24*, 3277.

(15) The absolute configuration of the major carboxylic acid was determined as (2*R*,3*R*) by comparison of the optical rotation of the corresponding methyl ester **9a** with the related compound reported in ref. 5a. Furthermore, the dihydrobenzofuran **9a** was independently synthesized by utilizing Evans' asymmetric aldol reaction and subsequent acidic cyclization to confirm the stereochemistry. For Evans' enantioselective aldol reaction, see: Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(16) We have recently completed the total synthesis of (–)-ephedradine A (**4**). Full details of the total synthesis of **4** will be reported in due course.